ANDREWS OFFICE PRODUCTS CAPITOL HEIGHTS, MD (K)

CHRONOLOGY OF FDA APPROVAL OF KANEKA'S LA-15 PMA

Date	Action
11/29/85	Kaneka submits application for LA-40 Investigational Device Exemption ("IDE") No. G850224 ("LA-40 IDE")
4/18/86	FDA approves Kaneka's LA-40 IDE
7/10/86	Kaneka initiates clinical study of Liposorber® LA-40 Column, i.e. first patient is treated under clinical study protocol
2/10/87	Correspondence to FDA providing information regarding Institutional Review Board ("IRB") approvals
3/5/87	FDA issues deficiency letter for Kaneka's 2/10/87 LA-40 IDE Supplement
5/5/87	Kaneka submits report regarding potential adverse device effect for LA-40 IDE
5/28/87	Letter from Dr. Kshitij Mohan of FDA regarding Kaneka's 5/5/87 report
3/14/88	Kaneka submits LA-15 IDE No. G880069 ("LA-15 IDE")
3/24/88	Kaneka submits LA-40 Application for Pre-Market Approval ("PMA") No. P880019 ("LA-40 PMA")
4/14/88	FDA issues deficiency letter for Kaneka LA-15 IDE
5/17/88	Kaneka submits LA-40 IDE Supplement regarding death of patient participating in clinical trials
6/10/88	Kaneka informally meets with FDA regarding LA-15 protocol
6/15/88	FDA requests additional information regarding Kaneka 5/17/88 LA-40 IDE Supplement
7/22/88	FDA issues deficiency letter for Kaneka's LA-40 PMA
7/25/88	Kaneka submits LA-40 IDE Supplement to extend clinical study
7/26/88	Kaneka submits LA-40 IDE Supplement providing additional information requested in FDA's 6/15/88 letter
9/16/88	Kaneka informally meets with FDA regarding further revisions to LA-15 protocol
9/20/88	Kaneka submits IDE amendments responding to deficiencies in FDA's 4/14/88 letter
10/21/88	FDA conditionally approves LA-15 IDE
10/25/88	Kaneka submits LA-40 IDE Supplement requesting authorization to conduct rebound study
11/13/88	Meeting of Kaneka's clinical investigators regarding initiation of LA-15 clinical studies
11/14/88	FDA approves Kaneka's 10/25/88 LA-40 IDE Supplement
12/19/88	Kaneka submits LA-15 IDE Supplement providing information and documentation requested in FDA's 10/21/88 grant of conditional approval

Date	Action
12/22/88	Kaneka initiates clinical study of Liposorber® LA-15 System, i.e. first patient is treated under clinical study protocol
1/17/89	FDA issues deficiency letter for Kaneka's LA-15 IDE
1/17/89	Kaneka submits Annual Progress Report for LA-40 IDE reporting additional safety and efficacy data for investigational treatments from initiation of study through 12/31/88
2/16/89	Kaneka submits LA-15 IDE Supplement providing information and documentation requested in FDA's 1/17/89 letter
2/16/89	FDA approves Kaneka's 1/17/89 LA-40 Supplement
3//7/89	Kaneka submits LA-40 IDE Supplement providing information and documentation regarding software development and validation requested in FDA's 2/16/89 letter
3/23/89	Kaneka submits LA-15 IDE Supplement providing English translations of Exhibits A through C to 2/16/89 IDE Supplement
4/7/89	Kaneka submits LA-40 IDE Supplement regarding death of patient participating in clinical trials
4/21/89	Letter from Dr. Helena Breslawec of FDA requesting summary of testing data and verification and validation protocols for LA-15 IDE
5/3/89	Correspondence to FDA staff submitting background information and documentation for software development and validation
5/5/89	FDA requests additional information regarding Kaneka 4/7/89 LA-40 IDE Supplement
5/22/89	Kaneka submits LA-15 IDE Supplement providing information and documentation requested in 4/21/89 FDA letter
6/2/89	Kaneka submits LA-40 IDE Supplement providing information and documentation regarding patient death requested in FDA's 5/5/89 letter
6/20/89	Letter approving LA-15 IDE and acknowledging satisfaction of previously stated conditions
7/24/89	Kaneka submits LA-15 IDE Supplement providing certification of IRB approvals
7/31/89	Kaneka submits LA-15 IDE Supplement informing FDA of certain modifications to the MA-01 Apheresis Machine, which controls the operation of the Liposorber® LA-15 System
8/25/89	FDA approves Kaneka's 7/31/89 LA-15 IDE Supplement
12/22/89	Kaneka submits amendment to LA-40 PMA
2/20/90	Kaneka submits IDE Supplement requesting expansion of clinical study patient population
3/21/90	FDA approves LA-15 IDE Supplement expanding clinical study patient population

Date	Action
3/22/90	Kaneka informally meets with FDA staff to review software validation materials
4/17/90	Kaneka submits Annual Progress Report for LA-15 IDE reporting additional safety and efficacy data for investigational treatments from initiation of study through 2/28/90
5/17/90	FDA requests additional information for 4/17/90 LA-15 IDE Annual Progress Report and Supplement
6/18/90	Kaneka submits LA-15 IDE Supplement providing information requested in FDA's 5/17/90 letter
7/12/90	Kaneka submits LA-15 IDE Supplement requesting authorization for compassionate or emergency use
7/16/90	FDA issues deficiency letter for Kaneka's LA-40 PMA
7/17/90	Kaneka informally meets with FDA staff regarding draft safety issues analysis for software validation
7/19/90	FDA approves Kaneka's 4/17/90 LA-15 IDE Supplement
9/21/90	Kaneka requests informal meeting with FDA staff to review LA-40 PMA deficiencies
12/11/90	Kaneka informally meets with FDA staff to review LA-40 PMA deficiencies
12/14/90	Kaneka meets with FDA regarding LA-40 PMA deficiency letter
2/6/91	Kaneka submits LA-15 IDE Supplementing requesting authorization to recover costs of devices and extending follow-up treatment phase for clinical trial
3/8/91	FDA approves Kaneka's 2/6/91 LA-15 IDE Supplement
3/26/91	Kaneka submits LA-15 PMA No. P910018 ("LA-15 PMA")
6/17/91	Kaneka submits Annual Progress Report for LA-15 IDE reporting additional safety and efficacy data for investigational treatments from 3/1/90 through 2/28/91
7/22/91	Meeting of Kaneka's clinical investigators to review status of ongoing LA-15 clinical studies
9/9/91	FDA issues deficiency letter for Kaneka's LA-15 PMA
10/2/91	In response to FDA's 9/9/91 letter, Kaneka requests that FDA file its LA-15 PMA
10/3/91	FDA files Kaneka's LA-15 PMA
10/28/91	Kaneka meets with FDA regarding LA-15 deficiency letter
11/12/91	Letter from Philip J. Phillips of FDA regarding filing and amendment of Kaneka's PMA
12/20/91	Kaneka submits amendment to LA-15 PMA responding to deficiencies

Date	Action
12/20/91	Kaneka submits to FDA Consensus Statement regarding the clinical utility of LDL cholesterol lowering in indicated patient population
2/27/92	Kaneka submits LA-15 IDE Supplement requesting extension of follow-up treatment under its clinical trial
3/3/92	Kaneka submits amendment updating LA-15 PMA to present safety and efficacy data from 1,088 additional LDL-apheresis procedures from 7/1/90 through 9/30/91
3/6/92	Kaneka responds to FDA request for information regarding LA-15 PMA
3/20/92	Letter from Dr. Lillian Yin of FDA requesting information regarding LA-15 IDE
3/30/92	FDA approves Kaneka's 2/27/92 LA-15 IDE Supplement and requests additional information
4/28/92	Kaneka submits LA-15 IDE Supplement in response to FDA's 3/20/92 request for information
4/28/92	Kaneka submits LA-15 IDE Supplement providing information requested in FDA's 3/30/92 letter
6/9/92	Kaneka submits Annual Progress Report for LA-15 IDE reporting additional safety and efficacy data for investigational treatments from 3/1/91 through 2/29/92
6/29-7/22/92	FDA representative conducts pre-approval inspection of manufacturing facilities for device components
7/27/92	Letter from Dr. Michael J. Blackwell of FDA requesting information regarding LA-40 IDE
9/3/92	Kaneka informally meets with FDA to discuss the clinical utility of lowering LDL cholesterol in homozygote and severe heterozygote patients
9/10/92	Kaneka submits LA-40 IDE Supplement providing information requested in FDA's 7/27/92 letter
9/18/92	Kaneka submits LA-15 IDE Supplement identifying a domestic source of 5% sodium chloride injection, USP
10/16/92	FDA conditionally grants 9/18/92 LA-15 IDE Supplement
10/19/92	Kaneka informally meets with FDA to discuss and define more precisely the patient population with severe familial hypercholesterolemia for whom treatment with the Liposorber® LA-15 System would be indicated
11/12/92	Kaneka submits report of potential unanticipated adverse device effect for LA-15 IDE
11/13/92	Kaneka submits "Target Patient Population: Definition and Explanation," a revised definition of indicated patient population with detailed explanation summarizing the findings of previously reported studies and other data

Date	Action
12/1/92	Kaneka submits LA-15 IDE Supplement providing information requested in FDA's 10/16/92 letter
12/16/92	Kaneka appears before Gastroenterology and Urology Devices Panel
4/26/93	Kaneka submits letter to Robert R. Gatling, Jr. summarizing its prior submissions to FDA and urging formal FDA response to Kaneka's 12/20/91 amendment
5/27/93	Kaneka submits follow-up report of potential unanticipated adverse device effect
6/11/93	Kaneka submits Annual Progress Report for LA-15 IDE reporting additional safety and efficacy data for investigational treatments from 3/1/92 through 2/28/93
6/23/93	Kaneka informally meets with FDA (at request of FDA staff) to review clinical utility and indicated patient population que4stions raised by FDA
6/25/93	Kaneka submits letter to Robert R. Gatling, Jr. of FDA indexing the substantive topics of Kaneka's LA-15 PMA submissions in accordance with the agenda items of 6/23/93 meeting
6/25/93	Letter from Robert R. Gatling, Jr. of FDA requesting additional information regarding Kaneka's 11/12/92 and 5/27/93 reports for LA-15 IDE
7/13/93	Letter from Dr. Lillian Yin requesting additional information regarding LA-15 IDE
8/6/93	Kaneka submits LA-15 IDE Supplement providing information and documentation requested in FDA's 6/25/93 letter
8/13/93	Kaneka submits LA-15 IDE Supplement providing information requested in FDA's 7/13/93 letter
9/3/93	Letter from Dr. Lillian Yin of FDA requesting additional information regarding Kaneka's 8/6/93 LA-15 IDE Supplement
10/18/93	Kaneka submits LA-15 IDE Supplement providing information requested in FDA's 9/3/93 letter
11/17/93	Letter from Dr. Lillian Yin of FDA requesting additional information regarding unanticipated adverse device effect
12/20/93	Kaneka submits letter to FDA requesting formal response to its 12/20/91 and 3/3/92 submissions and requesting informal meeting with FDA staff to address any open issues
12/20/93	Kaneka submits LA-15 IDE Supplement providing information and documentation requested in FDA's 11/17/93 letter
5/19/94	Letter from Dr. Lillian Yin of FDA requesting additional information regarding Kaneka's LA-40 IDE
5/23/94	Kaneka informally meets with FDA

Date	Action
6/15/94	Kaneka submits amendment of LA-15 PMA
7/5/94	Kaneka submits letter to Dr. Lillian Yin of FDA responding to 5/19/94 letter regarding LA-40 IDE
7/18-7/25/94	FDA representative conducts pre-approval inspection of manufacturing facilities for device components
7/19/94	Kaneka submits Annual Progress Report for LA-15 IDE reporting additional safety and efficacy data for investigational treatment from 3/1/93 through 2/28/94
7/25/94	Letter from Dr. Lillian Yin of FDA requesting final report for LA-40 IDE
9/8/94	Kaneka submits LA-40 IDE Supplement responding to FDA's 7/25/94 letter
11/4/94	Kaneka submits report for LA-15 IDE in connection with patient death
11/11/94	Kaneka submits final report for LA-40 IDE
11/22/94	Kaneka submits letter requesting Advisory Panel consideration of LA-15 PMA
11/23/94	FDA staff informally requests chart of information in LA-15 PMA
12/2/94	Letter from Dr. Lillian Yin of FDA requesting information regarding 11/4/94 IDE Supplement
12/6/94	Kaneka submits amendment of LA-15 PMA providing information and documentation requested by FDA staff in its 11/23/94 informal request
1/17/95	Kaneka submits LA-15 IDE Supplement providing information and documentation requested in FDA's 12/2/94 letter
2/17/95	FDA issues additional deficiency letter for Kaneka's LA-15 PMA
3/14/95	Kaneka submits amendment of LA-15 PMA responding in part to FDA's 2/17/95 deficiency letter, providing expedited responses to certain deficiencies as requested by FDA staff
3/15/95	Correspondence to FDA forwarding diskette of summary of safety and effectiveness
3/24/95	Kaneka submits amendment of LA-15 PMA responding in part to FDA's 2/17/95 deficiency letter, providing expedited responses to certain additional deficiencies as requested by FDA staff
3/24/95	Correspondence to FDA forwarding 18 copies of selected volumes from Kaneka's 6/15/95 LA-15 PMA amendment as requested by FDA staff
4/21/95	Gastroenterology and Urology Devices Panel recommends LA-15 PMA for approval
5/18/95	Informal correspondence from FDA requesting additional information

Date	Action
6/8/95	Kaneka submits amendment of LA-15 PMA responding in part to FDA's 2/17/95 deficiency letter, providing responses to all remaining deficiencies other than revised labeling
7/5/95	Kaneka submits amendment of LA-15 PMA providing revised labeling for the Liposorber® LA-15 System and its disposable device components
8/2/95	Kaneka submits Annual Progress Report of LA-15 IDE reporting additional safety and efficacy data for investigational treatments from 3/1/94 through 2/28/95
8/3/95	FDA staff informally requests additional information and/or modifications to Kaneka's existing submission
8/7-8/25/95	FDA representative conducts pre-approval inspection of manufacturing facilities for device components
8/16/95	FDA staff informally requests additional information and/or modifications to Kaneka's existing submission
9/1/95	Letter from Dr. Lillian Yin of FDA requesting additional information regarding Kaneka's Annual Progress Report
9/8/95	FDA staff informally requests additional information and/or modifications to Kaneka's existing submission
9/18/95	Kaneka submits amendment of LA-15 PMA providing information and documentation requested by FDA staff in its 8/3, 8/16 and 9/8 informal requests
9/22/95	FDA staff informally requests additional information and/or modifications to Kaneka's existing submission
9/26/95	FDA staff informally requests additional information and/or modifications to Kaneka's existing submission
9/27/95	Kaneka submits amendment of LA-15 PMA providing information and documentation requested by FDA staff in its 9/22 and 9/26/95 informal requests
9/27/95	Kaneka submits LA-15 IDE Supplement providing information requested in FDA's 9/1/95 letter
9/28/95	FDA staff informally requests update report for Kaneka's LA-15 PMA
9/29/95	Kaneka submits amendment of LA-15 PMA submitting Update Report which provides safety and effectiveness data for 2,458 additional investigational treatments performed during the period from 10/1/91 through 6/30/95
10/2/95	FDA staff informally requests revisions to labeling
10/3/95	Kaneka submits amendment of LA-15 PMA providing information and documentation requested by FDA staff in its 10/2/95 informal request

Date	Action
10/5/95	FDA informally requests revisions to Operator's Manual and Patient Guide
10/6/95	Kaneka submits amendment of LA-15 PMA providing information and documentation requested by FDA staff in its 10/5/95 informal request, including revised copies of Operator's Manual and Patient Guide
10/13/95	FDA issues approvable letter for Kaneka's LA-15 PMA
10/20/95	Kaneka submits amendment of LA-15 PMA confirming its concurrence with the "Conditions of Approval" as requested in 10/13/95 approvable letter
10/30/95	FDA staff informally requests additional information and/or modifications to Kaneka's existing submission
11/6/95	FDA staff informally requests additional information and/or modifications to Kaneka's existing submission
12/8/95	FDA staff informally requests additional information and/or modifications to Kaneka's existing submission
12/15/95	Kaneka submits amendment of LA-15 PMA providing information and documentation requested by FDA staff in its 10/30, 11/6 and 12/8/95 informal requests
1/30/96	Kaneka submits amendment of LA-15 PMA providing copies of further revised labeling in response to informal requests of FDA staff
1/30/96	Kaneka submits correspondence for LA-15 IDE regarding patient death
2/16/96	FDA staff informally requests additional information and/or modifications to Kaneka's existing submission
2/21/96	Kaneka submits amendment of LA-15 PMA providing information and documentation requested by FDA staff in its 2/16 informal request
2/21/96	FDA issues final approval letter